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Subject: Environmental Defense comments on Diglyme (CAS# 111-96-6)



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Environmental Defense appreciates this opportunity to submit comments on the robust summary/test plan for Diglyme (CAS# 111-96-6).

Ferro Corporation, in response to EPA's High Production Volume (HPV) Chemical Challenge, has submitted robust summaries and a test plan describing limited data to address SIDS elements required for diglyme. This is a very high production volume chemical. According to the test plan it is used as a solvent for certain plastics, as a reaction solvent for some alkali metals, in certain coatings and in photolithography, and for manufacture of semiconductor chips. Little information is provided regarding the production, transport or possible use(s) in consumer products that might result in human or environmental exposure to diglyme.

Review of the studies summarized in the test plan indicates that each of the SIDS elements for physical/chemical parameters and environmental fate of diglyme have been addressed by an appropriate reference or modeled data. These studies indicate diglyme is resistant to biodegradation, but the fact that it is miscible with water should limit its bioaccumulation. The SIDS elements for ecotoxicity and mammalian toxicity are each addressed by a single study described in the robust summaries. Most of these studies, particularly the "Methods" sections, are described in much more detail than necessary.

Whereas we are aware that the HPV Challenge only requires a single adequate study to be used to fill each SIDS element, diglyme has been the subject of considerable published research that needs to be incorporated into the robust summaries

On review of the studies cited, we question whether they are adequate to address the required SIDS elements. The quality of these studies is questionable; all of the ecotoxicity studies and most of the mammalian toxicity studies fail to describe the purity of the test compound. The only robust summaries that did describe the purity of the test compound were for the studies of repeat inhalation toxicity and developmental/teratogenicity.

The metabolism of diglyme is discussed at some length in the test plan, which points out that diglyme metabolism can follow two different pathways. One pathway results in the formation of 2-methoxyacetic acid the other does not. 2-Methoxyacetic acid is thought to account to for the reproductive toxicity of diglyme, and good evidence is presented to support that assumption. It is also mentioned that human microsomal preparations metabolize diglyme in the same manner as those from experimental animals. Inhalation studies described in the test plan have demonstrated that malformations were induced in low incidences in rats exposed to

concentrations as low as 25 ppm. Thus, it is of interest to know if diglyme is used in products that might result in consumer or general population exposure. Another fact not mentioned in the discussion of metabolism, and not shown in the metabolic scheme on page 14 of the test plan, is that the second metabolic pathway results in the formation of two molecules of methanol for each molecule of diglyme metabolized. Humans are much more sensitive to the toxicity of methanol than laboratory animals used in toxicity studies of diglyme. Therefore, diglyme metabolism to methanol and the possible greater sensitivity of humans to diglyme intoxication should be considered in any assessment of health risks associated with exposure to this chemical. Human intoxication is not likely to occur in the absence of direct consumption of diglyme, but, in case that should happen, some discussion of this point should be included in this section of the test plan.

The test plan proposes that no additional studies be conducted to address the SIDS elements required by the HPV Challenge. We do not agree unless the purity of the test compounds used in most studies of ecotoxicity and mammalian toxicity can be provided.

In summary, we recommend that this submission not be accepted unless the purity of the test compound used in each study cited can be verified. If the purity of the test compound cannot be provided for the studies described or other appropriate studies currently in the literature, then additional studies should be required. Also, while it is not required, we feel this submission would be much more useful if greater background information could be provided regarding possible sources of human and environmental exposure.

Thank you for this opportunity to comment.

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